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A review of transfusion- and trauma-induced hypocalcemia. Is it time to change the lethal triad to the lethal diamond?

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The preliminary ideas for this paper were presented by Ricky Ditzel at the Annual Meeting of the Committee for Tactical Emergency Casualty Care, May 13-17, 2018 in Charlotte, NC and at the 31st Annual Meeting of the Special Operations Medical Association's Special Operations Medical Scientific Assembly, May 6-10, 2019 in Charlotte, NC. The discussions generated by this presentation subsequently drove changes to the Joint Trauma System's Damage Control Resuscitation Clinical Practice Guideline.

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Abstract

The understanding of trauma management and damage control resuscitation is constantly changing as new research becomes available. While poor outcomes in hemorrhagic shock have traditionally been attributed to the "lethal triad" of hypothermia, coagulopathy, and acidosis, research has suggested that hypocalcemia may also play an integrated part in this interaction. Studies have shown a prevalence of hypocalcemia in trauma patients, as well as greater mortality associated with severe hypocalcemia in trauma. Given that whole blood is becoming the fluid of choice in resuscitation and that the citrate used to preserve blood products can worsen existing hypocalcemia, prompt management of hypocalcemia becomes even more of a concern. For these reasons, the authors of this paper suggest hypocalcemia in trauma patients may be of greater importance than originally believed and propose creating the "lethal diamond" of trauma comprised of hypocalcemia, acidosis, coagulopathy, and hypothermia. It is hoped that this increased focus on hypocalcemia in trauma can lead to research regarding early administration of calcium with the hopes of improving trauma patient outcomes.

Level of Evidence: Therapeutic/care management Level IV. Study Type: Review article.

Key Words: hypocalcemia, DCR, RDCR, resuscitation, lethal triad, blood transfusion, hemorrhagic shock

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Background

Traumatic coagulopathy and the effects of transfusion

The principles of managing patients suffering from hemorrhagic shock have evolved over time. It is well supported that patients who continue to suffer from shock—or hypoperfusion—are at greater risk of morbidity and mortality attributable to "blood failure" precipitated by hypothermia, coagulopathy, and acidosis.[1] These three conditions—hypothermia, coagulopathy, and acidosis—collectively known as the lethal triad, serve as the foundational physiologic insults that describe the mechanisms of action of disseminated intravascular coagulopathy and drive the current hemorrhagic shock resuscitation efforts.[2,3] Hypothermia, defined as a core temperature under 35°C, exerts deleterious effects on hemostasis by inhibiting thromboxane-A_2, causing a reduction in local vasoconstriction and platelet aggregation at the site of injury in addition to altering the rate at which enzymatic process' occur throughout the clotting cascade. Moreover, hypothermia is associated with a leftward shift of the oxygen-hemoglobin dissociation curve and a reduction in myocardial contractility, both leading to reduced tissue oxygenation and an increased state of oxygen debt. These mechanisms described above directly correlate with coagulopathy and acidosis as irreversible shock progresses throughout the lethal triad. Coagulopathy, traditionally regarded as an international normalized ratio (INR) ≥ 1.5 in an acute setting, may additionally be exacerbated by hemodilution of platelets and clotting factors through crystalloid infusions.[4,5] Lastly, acidosis, or serum pH < 7.36, is associated with a reduction in coagulation factor activity and increases in fibrin degradation rate and coagulation times, further exacerbating the traumatic hemorrhage induced coagulopathy.[6] It is through these mechanisms by which each element of the lethal triad overlaps upon the others. Although the use of whole blood and blood products has assisted in decreasing mortality for patients suffering from the

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lethal triad, the authors of this review believe that there are still gaps in the management of trauma-induced coagulopathy. The goal of this literature review is to demonstrate through examination of previous studies the prevalence of hypocalcemia in trauma and the need to address this deficiency in management of severely injured patients. From this, we hope to promote targeted research in the management of hypocalcemia in trauma and support recently published guidelines in trauma management that accounts for this gap in trauma-induced coagulopathy. We believe that early identification and correction of hypocalcemia in this patient population could be a missing link to the management and prevention of trauma-induced coagulopathy and effectively change the descriptor from the lethal triad to the Lethal Diamond.

Methods

In this review, initial studies were identified by searching Ovid for English language articles using the following key words: "hypocalcemia in trauma," "prehospital blood transfusion," and "hypocalcemia AND transfusion." Additional studies were then identified from the reference lists of the most relevant studies and were reviewed by two members (RMD and JLA) of the research team for relevance.

23 records were ultimately identified through this method; five articles were excluded due to lacking information related to hypocalcemia and one was later excluded due to not adding any additional conclusions that had not been previously covered. Information on the studies utilized in this review can be found in Table 1.

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Results

Trauma-related Hypocalcemia

Webster et al.[7] noted that 55% of trauma patients in a major trauma center in the UK were hypocalcemic (iCa<1.12 mmol/L) on arrival to the emergency department (ED) prior to the administration of any blood products. Magnotti et al.[8] also noted hypocalcemia on arrival of trauma patients to the ED, in which 56% of patients had an ionized calcium of less than 1.0 mmol/L (332/591) upon admission. This group, identified as lo-Cal, was associated with higher mortality (15.5% vs. 8.7%, p =0.036) and increased need for multiple (≥5 units PRBCs in 24 hours; 17.1% vs. 7.1%, p =0.005) and massive transfusions (≥10 units PRBCs in 24 hours; 8.2% vs. 2.2%, p =0.017). Magnotti et al.[8] concluded that low ionized calcium levels on admission to the ED was a useful independent predictor for the need for multiple transfusions on trauma patients.

Transfusion-related Hypocalcemia

Giancarelli et al.[9] noted that 97% of trauma patients receiving massive transfusion experience hypocalcemia, with 71% of those experiencing "severe hypocalcemia," with an ionized calcium level of less than 0.90 mmol/L. The severe hypocalcemia group was noted to have lower platelets (176 [CI 108-237] versus 208 [CI 169-272], p =0.003), lower pH (7.14 [CI 6.98-7.28] versus 7.23 [CI 7.14-7.33], p =0.019), and higher mortality (49% versus 24%, p =0.007) than the group with an ionized calcium greater than 0.90 mmol/L. Those in the severe hypocalcemia group also received more units of blood products (34 [CI 23-58] versus 22 [CI 18-30] units, p <0.001). Neither group ever reached a median ionized calcium of 1.12 mmol/L.

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Kyle et al.[10] came to the same conclusion in a separate research study looking at UK military casualties and their ionized calcium levels on arrival to a treatment facility after receiving blood products en-route. Hypocalcemia (iCa<1.12 mmol/L) among those in the non-treatment group—those who did not receive calcium concurrently with prehospital blood products—was 70% (166/237).

Webster et al.[7] noted that once patients began to receive blood products, the incidence and severity of hypocalcemia increased. Pre-transfusion, ionized calcium levels were 1.11 (95% CI 1.09-1.14 mmol/L), and after "any amount of blood product," 89% (33/37) of patients were hypocalcemic, with a post-transfusion ionized calcium level of 0.98 mmol/L (95% CI 0.93-1.02 mmol/L, p <0.001).

Mackay et al.[11] looked at trauma patients admitted to an ED who were anticipating receiving a massive transfusion and noted 85% (35/41) of total patients experienced some level of hypocalcemia (iCa<1.0 mmol/L), with 36.6% (15/41) experiencing "extreme hypocalcemia" (iCa<0.86 mmol/L) at some point during their treatment. Those in the "extreme hypocalcemia" group had more units transfused (median units transfused 14 [8-20] versus 5 [3-7]) and a higher mortality (60% versus 4%, p<0.01) compared to the "no extreme hypocalcemia group," providing another example of a "dose response of calcium level to blood products."[15] Of note, the researchers also noted that mortality increased in patients with hypercalcemia (iCa>1.25 mmol/L) either on admission or who reached it due to overcorrection by clinicians, with mortality reaching 78% (7/9, p<0.01). The total patients who experienced hypercalcemia during some phase of their treatment was 22% (9/41).[11]

Ho and Leonard[12] also noticed increased mortality associated with hypocalcemia from bleeding patients requiring massive transfusion (≥10 units of allogenic packed RBCs or whole blood),

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showing an "inverse concentration-dependent relationship" between the two after initiation of massive transfusion (odds ratio [OR] 1.25 per 0.1 mmol/l decrement, 95% CI 1.04-1.52, p=0.02).

Discussion

Today, the concepts of damage control resuscitation (DCR)[13] and remote damage control resuscitation (RDCR) are well documented and supported. It is suggested that the resuscitative fluid of choice for DCR and RDCR is whole blood (WB) as shown by Kornblith et al.[14] This study compared the hemostatic potential of WB to that of reconstituted WB (1:1:1 or 2:1:1 PRBC: fresh frozen plasma: platelets) and crystalloids, showing that WB was superior to both component therapy and crystalloid therapy for hemostatic potential. Similar results were seen in a retrospective study of combat casualties in Afghanistan who received blood transfusions conducted by Shackleford et al.[15], including a three-fold decrease in 30-day mortality compared to the not-transfused group. This data is included in Table 2.

In addition to the bleeding itself causing patients to suffer from hypocalcemia, the treatment for hemorrhagic shock—blood products—is further exacerbating the problem. This is due to the citrate present in blood products.

Both WB and RBCs are stored using citrate as the anticoagulant, where 3g of citrate are used per one unit of RBC and 1.66g of citrate are used per unit of WB stored with Citrate Phosphate Dextrose Adenine (CPDA-1).[16,17] Citrate works by chelating calcium in the blood.[16] During the clotting cascade, the release of calcium occurs after platelet adhesion, where it binds to phospholipids that appear after the activation of platelets and functions as a binding point for other coagulation factors.[16] Figure 1 details the different points in the coagulation cascade where ionized calcium is utilized.[18]

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Once in the body, citrate is metabolized in the liver, where it is converted into bicarbonate. A healthy adult can metabolize 3g of citrate in five minutes. However, in instances of decreased liver function (e.g., following trauma) or during a transfusion rate greater than one unit over five minutes, ionized calcium levels in the patient begin to decrease due to the ionized calcium in the blood being chelated by the free-floating citrate.[16] This condition is exacerbated more quickly when transfusing components (over WB) due to the increased amount of citrate in component therapy.[19]

As serum calcium levels drop, coagulopathy occurs, which can lead to continued hemorrhage and possible death.[16] The Kyle et al.[10] study suggested "there was a dose response of calcium level to blood products with a significant decrease in calcium levels as the volume of blood products increased."[10] Again, as similar to the Kyle et al.[10] study, Webster et al.[7] showed that the more units of blood that were given, the lower the ionized calcium levels that were seen in patients.

Both trauma itself as well as transfusion of blood are associated with worsening hypocalcemia. What is the significance of this? As stated above, Giancarelli et al.[9] noted patients in the "severe hypocalcemia" group had a higher mortality than those with an ionized calcium above 0.90 mmol/L on admission. Magnotti et al.[8] noticed higher mortality with ionized calcium levels of less than 1.0 mmol/L. Hästbacka and Pettilä[20] also concluded that a low ionized calcium level on admission of critically ill patients to an intensive care unit (ICU) was associated with increased mortality, showing hazard ratios of 5.1 (95% CI 2.9-9.0) for severe (<0.90 mmol/L) and 1.8 (95% CI 1.3-2.4) for mild ionized hypocalcemia (0.90-1.15 mmol/L). In addition, Cherry et al.[21] noted mortality was significantly increased in trauma patients with an ionized calcium of less than or equal to 1.0 mmol/L "regardless of age or injury severity" (26.4% versus 16.7%, p <0.05;

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OR 1.92) upon admission. While none of these studies prove causation, the evidence for correlation, at least, is overwhelming. This evidence suggests the importance of early management of hypocalcemia in trauma patients may be of more significance than previously believed.

Knowing that low ionized calcium levels on admission to an ED is associated with higher mortality, Kyle et al.[10] assessed whether early intravenous administration of calcium in the prehospital environment given concurrently with blood products had any impact on ionized calcium levels upon admission to the military treatment facility. Hypocalcemia in the treatment group, which received 10mL of calcium chloride intravenously, was 28.3% (17/60) compared to 70% of those in the non-treatment group who received blood products without calcium (166/237). Only 26.6% (63/237) of those in the non-treatment group had ionized calcium levels within normal limits compared to 41.7% (25/60) of those in the treatment group. Of note, patient mortality information was not included in this study.

Current US Military Protocols

The Joint Trauma System (JTS) released an updated Clinical Practice Guideline (CPG) for DCR during the review process for this manuscript that states a gram of calcium should be administered to patients "in hemorrhagic shock during or immediately after transfusion of the first unit of blood product and with ongoing resuscitation after every 4 units of blood products."[22] This CPG then recommends ionized calcium should be monitored and treated if it drops below 1.20 mmol/L.[22]

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The Lethal Diamond

Early, systematic management of these factors may lead to better outcomes for trauma patients. It is the belief of these authors that the lethal triad may be leaving out one other crucial factor that interacts with these other three conditions to the detriment of the trauma patient: hypocalcemia. We propose a new leg to the lethal triad, making a "lethal diamond," in which the four arms are coagulopathy, hypothermia, acidosis, and hypocalcemia. Hypocalcemia works as a functional piece in this diamond by interacting with the other three conditions as they do each other in the lethal triad. Coagulopathy occurs as calcium levels drop because the extrinsic, intrinsic, and central clotting cascade pathways rely on proper levels of ionized calcium in the blood.[9] Furthermore, these same receptors necessary for clotting that require ionized calcium can also be blocked by hydrogen ions since it is a competitive receptor antagonist.[23] Lower levels of ionized calcium in the blood are also associated with lower pH, increasing acidosis. Hypothermia decreases liver metabolism, which is important to metabolize citrate as it is introduced to the patient through transfusion.[24] Lastly, proper ionized calcium levels are necessary for the cardiac myocytes to properly function. Since they rely on a calcium-induced calcium release, low levels of ionized calcium reduce the heart's ability to properly contract. This problem also adds to the other three factors of the current lethal triad.[25] This information is depicted below in Figure 2.

By including hypocalcemia in the "lethal diamond," it is the hope of these authors that this will emphasize the need for early management of ionized calcium levels in trauma patients, to prevent or minimize the presence and severity of hypocalcemia. Though MacKay et al.[11] did notice increased mortality associated with hypercalcemia, due to either natural or iatrogenic causes, the conclusions ascertained above stress the importance of hypocalcemia management, while being cognizant of over-treating to the point of hypercalcemia. These authors propose the

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JTS DCR CPG to become the current standard for treating patients suffering from hemorrhagic shock, with the addition of ensuring ionized calcium levels do not exceed 1.25 mmol/L, due to the data from the MacKay et al. study.[11, 22] However, currently there is a knowledge gap on whether early administration of calcium products to serious trauma patients expecting to receive a transfusion has any impact on patient mortality. The inverse relationship between ionized calcium level on admission to an ED and patient mortality does not necessarily guarantee that early administration of calcium will correct this problem. While low ionized calcium levels have been associated with increased mortality, it is not clear whether the low ionized calcium is a cause of this outcome or just a predictor of it.

As seen in Table 1, there are currently, to these authors' knowledge, zero prospective randomized, controlled trials (RCT) focused on patient-centered outcomes concerning early calcium administration to bleeding trauma patients requiring transfusion. Therefore, targeted research is needed to determine if the early management of hypocalcemia in trauma can have a positive impact on patient mortality.

Conclusion

Thus far, the following has been established: over half of trauma patients are hypocalcemic prior to receiving any blood products on arrival to an ED[7,8]; transfusions further increase the severity of hypocalcemia, with more units transfused correlating to worsening ionized calcium levels[7-12]; lower ionized calcium levels on admission to an ED are associated with increased mortality[8,9,20,21]; and early administration of calcium products concurrently with blood product administration has been associated with a higher ionized calcium level on admission to an ED.[10] A double-blinded placebo-controlled randomized trial is needed to determine whether this is correlation or causation. It is the hope of these researchers that this review will promote interest

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in conducting this study and result in better outcomes for trauma patients using the "lethal diamond" as a reference, focusing on early administration of calcium products to trauma patients expected to receive transfusion. The authors also believe that existing research networks in the military and civilian prehospital and trauma systems will be instrumental in generating this study.

Limitations

Due to the time-sensitive nature of trying to initiate a prospective trial looking toward patient-centered outcomes of early calcium administration to trauma patients, the authors elected to not perform a full systematic review so we could publish our search of the available data. The concept of the lethal diamond cannot be proven until a prospective, double-blind, placebo-controlled randomized control study has been completed and published. As such, there are concerns about study limitations of the available literature.

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Disclosure

The authors declare no conflicts of interest. No funding received in writing this piece.

Author Contribution

Ricky Ditzel conceived of the presented idea and first developed the theory. Justin Anderson conducted the literature search and wrote the manuscript with the help of the other authors. All authors discussed the results and contributed to the final manuscript.

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Figure Legends:

Figure 1. "Present model of 'cell-based' coagulation according to Hoffman and the target location of ionized calcium"[18]

Figure 2. Demonstration of the interaction of calcium with the other aspects of the Lethal Diamond[9, 23-25]

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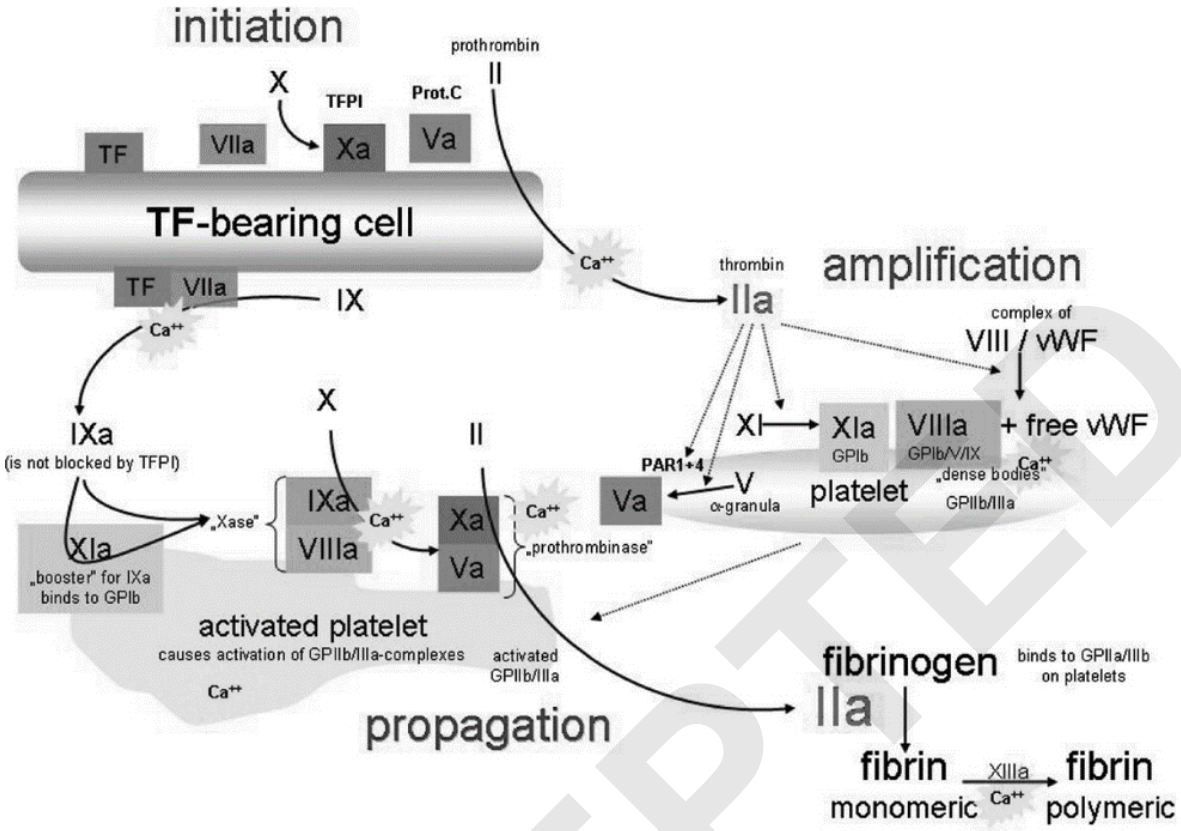

Figure 1. "Present model of 'cell-based' coagulation according to Hoffman and the target location of ionized calcium"[18]

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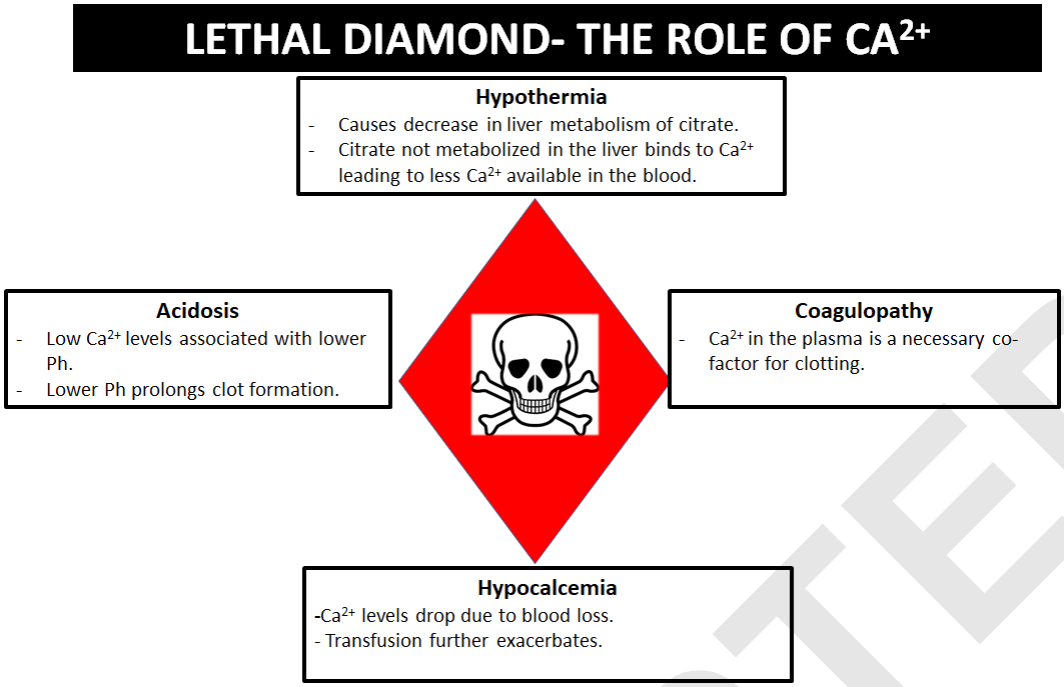
LETHAL DIAMOND- THE ROLE OF CA2+
Hypothermia
- Causes decrease in liver metabolism of citrate.
- Citrate not metabolized in the liver binds to Ca2+ leading to less Ca2+ available in the blood.
Acidosis
- Low Ca2+ levels associated with lower Ph.
- Lower Ph prolongs clot formation.
Coagulopathy
- Ca2+ in the plasma is a necessary co-factor for clotting.
Hypocalcemia
-Ca2+ levels drop due to blood loss.
- Transfusion further exacerbates.

Figure 2. Demonstration of the interaction of calcium with the other aspects of the Lethal Diamond[9, 23-25]

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Table 1. Information of studies included in review				
Author	**Publication Year**	**Publication Type**	**Primary Outcome**	**Number of patients**
Armand R et al.	2003	Review	N/A	N/A
Hästbacka J et al.	2003	Retrospective	30-day mortality	941
Cherry RA et al.	2006	Retrospective	in-hospital mortality	396
Holcomb JB et al.	2007	Special Commentary	N/A	N/A
Lier H et al.	2008	Review	N/A	N/A
Spinella PC et al.	2009	Review	N/A	N/A
Ho KM et al.	2011	Retrospective	in-hospital mortality	352
Magnotti LJ et al.	2011	Observational	in-hospital mortality	591
Kornblith LZ et al.	2014	Prospective (blood)	Multiple Lab Values	34
Fisher AD et al.	2015	Special Commentary	N/A	N/A
Li K et al.	2015	Retrospective	Mean citrate	267

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Bjerkvig CK et al.	2016	Review	N/A	N/A
Giancarelli A et al.	2016	Retrospective	iCa Lab Value	156
Webster S et al.	2016	Retrospective	iCa Lab Value	55
Kyle T et al.	2017	Retrospective	iCa Lab Value	297
MacKay EJ et al.	2017	Observational	in-hospital mortality	41
Shackelford SA et al.	2017	Retrospective	24-hour/30-day mortality	502

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Table 2. Medevac Study Population post-treatment Characteristics and Outcomes

Unadjusted post-treatment Between-groups difference	Transfused Pre-hospital	Not Transfused Pre-hospital	*p* value*
***KIA (%)**	2 (3.8%)	58 (20.3%)	0.003*
***Died (KIA + DOW) within 24 hours of MEDEVAC take-off from POI (%)**	2 (3.8%)	64 (22.4%)	0.001*
***Died (KIA + DOW) within 30 days**	5 (9.4%)	77 (26.9%)	0.005*
***Tranexamic Acid [TXA] (%)**	48 (90.6%)	144 (50.3%)	<0.001*
Documented Shock [SBP <90, HR>120, or shock index >0.09] upon ED arrival (%)	N=52 39 (75%)	N=233 137 (63%)	0.11
***Massive Transfusion [>10 units/24 hours] (%)**	40 (75%)	119 (42%)	<0.001*
ISS: Median (IQR)	29 (17, 36)	24 (17, 36)	0.179
AIS Score indication torso hemorrhage (%)	22 (41.5%)	108 (37.8%)	0.646

***Statistically significant at <0.05 level by Fisher's exact test.**

Abbreviations

Table 2: KIA, killed in action; DOW, Died of wounds; MEDEVAC, medical evacuation; POI, point-of-injury; SBP, systolic blood pressure; HR, heart rate; ED, emergency department; ISS, injury severity score; IQR interquartile range; AIS, abbreviated injury scale

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